Medical and Pediatric Oncology 29:36–40 (1997)

Diabetes Insipidus Secondary to Langerhans' Cell Histiocytosis: Is Radiation Therapy Indicated?

Kenneth E. Rosenzweig, MD, Robert J. Arceci, MD, PhD, and Nancy J. Tarbell, MD*

Langerhans' cell histiocytosis (LCH) is a proliferative disease of Langerhans' cells that has multiple clinical manifestations including diabetes insipidus (DI). This study reviews the effectiveness of hypothalamic-pituitary radiation therapy (HPRT) as a treatment of LCH-induced DI in the modern era. A retrospective review was done of 116 pediatric patients with LCH seen from 1975 to 1992. Seventeen of the 116 patients (15%) were diagnosed with complete or partial diabetes insipidus. Diagnosis was made either by water deprivation test or on clinical grounds. Fourteen patients received hypothalamic-pituitary irradiation as treatment for DI. The median interval from the onset of DI symptoms (polyuria and polydipsia) to treatment was 30 days. The median interval from the onset of diagnosis to treatment was 4 days. With a mean follow-up of 7.3 years (range, 2.4–14.3), only two patients had a complete response to therapy, as defined as no need for antidiuretic hormone (ADH) replacement therapy. No patient had a partial response, defined as a decrease in the dose of ADH replacement. Of the two responders, neither had a complete ADH deficiency, suggesting ''early'' disease. In addition, both received RT within 3 days.

We feel that the standard treatment of RT to all patients with LCH-induced DI is no longer justified. Our series has shown no benefit in treating patients with a long history of DI. Rather, an improved rationale would be rapid initiation of hypothalamic-pituitary irradiation in patients with new symptoms of DI and an abnormal water deprivation test. Med. Pediatr. Oncol. 29:36–40, 1997.

Key words: diabetes insipidus; Langerhans' cell histiocytosis; histiocytosis X; radiation therapy; radiotherapy; pediatric oncology

INTRODUCTION

Langerhans' cell histiocytosis (LCH) encompasses several disorders previously known as histiocytosis X, Letterer-Siwe disease, Hand-Schüller-Christian syndrome, eosinophilic granuloma of bone, and self-healing reticulohistiocytosis [1,2]. The normal epidermal Langerhans' cell is a dendritic, antigen-presenting cell characterized by the intracytoplasmic Birbeck granule and by expression of CD1 a glycoprotein [3]. Tissue damage is caused by excessive production of cytokines and prostaglandins [4].

Diabetes insipidus (DI) is a relatively common manifestation of LCH. Different series report a 5–50% prevalence among patients with LCH. An etiology of DI is thought to be infiltration of the posterior pituitary or hypothalamus by Langerhans' cells, which causes local tissue damage. Function may be disrupted by the physical infiltration of cells or by the excessive production of interleukin-1 and prostaglandin E_2. At diagnosis, symptoms of DI are present in less than one-third of the children with LCH who will eventually develop DI. Later onset of DI occurs within 4 or 5 years of diagnosis [5].

Diabetes insipidus can be diagnosed by clinical evaluation (polydipsia and polyuria with low urine osmolality) or by water deprivation test. In a water deprivation test, patients can be classified as having a full or partial antidiuretic hormone (ADH) deficiency based on their urine osmolality and response to exogenous ADH [6,7].

The drug of choice in the treatment of DI is exogenous ADH given by a nasal tube or spray delivery system [6,7]. Hypothalamic-pituitary radiation therapy (HPRT) has historically been used as a treatment for LCH-induced DI [8], although it remains controversial [9].

Given our institution's previous report stressing the value of urgent irradiation in the treatment of all patients with LCH-induced DI [10], the purpose of this study is to review our last 20 years of experience in treating patients and to better define those who might benefit from radiation therapy.

Dr. Arceci is affiliated with Children's Hospital Medical Center, Cincinnati, Ohio.

Joint Center for Radiation Therapy, Department of Radiation Oncology, Children's Hospital, Boston, Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

*Correspondence to: Nancy Tarbell, MD, Massachusetts General Hospital, Bullfinch Building, Room 360A, Boston, MA 02114.

Received 17 June 1996; Accepted 5 July 1996

METHODS

The charts of 116 consecutive pediatric patients seen at the Joint Center for Radiation Therapy, Children's Hospital, Boston, and the Dana Farber Cancer Institute from 1975 to 1992 were retrospectively reviewed. Our institution's experience with LCH has previously been reviewed for patients who presented prior to 1975 [10]. There is no overlap between this previous study and the current patient population.

Twenty-six patients developed symptoms of polyuria and polydipsia. Six of these patients had negative water deprivation studies and resolution of their symptoms. Three patients had been treated at outside institutions with HPRT (all without response) prior to the initial presentation at our institution and were excluded from this study. Seventeen patients (15% of total patient population) received the diagnosis of complete or partial diabetes insipidus confirmed either by water deprivation studies (59%) or on clinical grounds (41%). Nine of the patients with DI had the diagnosis of LCH prior to developing symptoms of DI.

Of the seventeen patients with the diagnosis of DI, fourteen received HPRT. For three of these patients, HPRT and surgical control of bone lesions was the only treatment of their disease. One patient received thymic humoral factor as his only chemotherapeutic agent [11]. Ten patients received cytotoxic chemotherapeutic agents and prednisone as treatment of their LCH. Two of these patients, both with long histories of polyuria and polydipsia prior to presentation and other manifestations of disease, received concurrent HPRT and chemotherapy. The remaining patients had no change in their chemotherapy regimens after the diagnosis of DI.

HPRT was given via megavoltage radiation to the hypothalamic-pituitary axis via opposed lateral beams. Portal size was 5 cm × 5 cm − 7 cm × 7 cm. As in other studies [6,10], a complete response (CR) was defined as the patient requiring no further ADH replacement and a partial response (PR) was defined as a decrease in the dose of ADH replacement therapy.

RESULTS

Fourteen patients with LCH-induced DI (LCH-DI) were treated with HPRT. The median age at the time of LCH diagnosis was 20 months (range, 5 months–16.3 years) and the median age of onset of DI symptoms was 37 months (range, 1 month–13.3 years). Four patients had symptoms of DI for as long as 6 years before the biopsy proven diagnosis of LCH. Nine patients had the diagnosis of LCH for a median time of 24 months (range 11–55 months) prior to the onset of DI symptoms.

The median interval from the onset of DI symptoms (polyuria and polydipsia) to treatment was 30 days. The median interval from the onset of diagnosis to treatment was 4 days. With a mean follow-up of 7.3 years (range 2.4–14.3 years), only two patients (14%) had a complete response to radiation therapy (Table I). One patient had a partial response after an initial treatment of 600 cGy in three fractions and subsequently received an additional 1,200 cGy in four fractions and developed a complete response. The other patient had a normal water deprivation test and subsequently developed increased polyuria and polydipsia and was rapidly treated based on the clinical presentation. Both responses occurred within one month of the end of radiation and there was no subsequent relapse of symptoms while off treatment. The three patients with DI who did not receive HPRT were diagnosed and given ADH replacement within 30 days of initial symptoms. One of these patients also received cytotoxic chemotherapy and prednisone after diagnosis of DI. With a follow-up of 4.3–5.8 years, all three remain on ADH replacement.

Twelve patients were alive without disease at the time of last follow-up. One patient developed, and died from, a hypothalamic astrocytoma 29 months after receiving 800 cGy in three fractions. He had clinically active LCH at death which was confirmed at necropsy. One patient continues to have active systemic disease requiring cytotoxic chemotherapy.

Twelve patients (86%) had skin disease in addition to DI. Other common sites of involvement include bony lesions in the skull (50%) and otitis (29%). Only one patient had disease in the lung, which has previously been associated with LCH-induced DI [6]. Two patients (14%) had panhypopituarism after receiving HPRT and 12 patients (86%) had no complications subsequent to HPRT.

DISCUSSION

Treatment Response

There is a long history of the use of radiation in the treatment of LCH-induced DI. In a review of patients treated at Children's Hospital, Boston, Greenberger et al. report [8] one patient from 1918 who was treated with radiation to the sella for LCH-induced DI. In 1956, Dealy and Sosman of Peter Bent Brigham Hospital reported ''several instances'' in which LCH-DI was controlled with HPRT and they estimated that one-third of patients achieved a complete remission [12]. However, there have been relatively few reports on the role of HPRT in the treatment of LCH-DI, most likely due to the rarity of this disorder. A review of the literature of the past 25 years is presented in Table II [5–7,10,13,14].

In patients receiving HPRT as a treatment of LCH-DI, Greenberger et al. [8] report a complete response (defined as the ability to discontinue ADH replacement therapy) in 19% of patients and a partial response (de-

TABLE I. Patients With LCH-Induced DI Treated With Hypothalamus-Pituitary Radiation Therapy (HPRT)

Patients	Age LCH diagnosed	Age DI symptoms	Dx[a]	Sx → Rx[b]	Dx → Rx[c]	Dose (fx)[d]	ADH Rx[e]	F/U from HPRT	Status	Complications	Other sites
1	18 mo	4.5 yr	F	90 d	4 d	750 (3)	↑	8.7 yr	AsD[h]	—	skin, BM, spleen
2	18 mo	6.1 yr	P	24 d	3 d	600 (3), 1,200 (4)	Off	9.5 yr	AsD	—	skin, otitis, lung
3	21 mo	32 mo	P	6 d	0 d	1,440 (8)	↑	14.3 yr	AsD	—	skin, skull otitis
4	19 mo	3.3 yr	F	20 d	12 d	750 (3)	↑	13.1 yr	AsD	panhypopituitarism	skin, skull, otitis, proptosis
5	16.3 yr	10.3 yr	C	8 yr	2 yr	1,800 (9)[i]	no Δ[e]	3 yr	AsD	—	skin
6	35 mo	1 mo	C	2.8 yr	8 d	600 (3)[j]	↑	7.8 yr	AsD	—	skin, skull, dental, proptosis
7	9 mo	24 mo	F	56 d	1 d	800 (3)	no Δ	8 yr	AsD	—	skull
8	13.3 yr	13.3 yr	C	45 d	14 d	750 (3)	no Δ	5.5 yr	AsD	—	skin
9	28 mo	25 mo	F	90 d	8 d	800 (4)	↑	29 mo	DcD[1]	astrocytoma	skin
10	10 mo	35 mo	C	—	—	750 (3)	no Δ	8.7 yr	AsD	—	skin, skull, otitis, dental
11	20 mo	3 yr	F	3 d	0 d	800 (4)	↑	6.8 yr	AsD	—	skin, skull, dental
12	3.3 yr	3.2 yr	C	5 d	1 d	800 (4)	Off	6.7 yr	AsD	—	skull, bone
13	26 mo	5.4 yr	P	8 d	1 d	600 (4)	↑	5.8 yr	AsD	—	skin
14	5 mo	29 mo	F	30 d	1 d	600 (4)	↑	4.2 yr	AcD[g]	panhypopituitarism	skin, skull, dental, lung, bone
Median	20 mo	37 mo		30 d	4 d	750 (3)		7.3 yr			

[a]Dx, type of diagnosis (F, full ADH deficiency) on water deprivation test; P, partial ADH deficiency on water deprivation test; C, clinical diagnosis.
[b]Sx → Rx, symptom to treatment interval.
[c]Dx → Rx, diagnosis to treatment interval.
[d]fx, number of fractions.
[e]ADH Rx, change in ADH replacement dose no Δ unchanged.
[f]F/U, follow-up.
[g]AcD, alive with disease (other than DI).
[h]AsD, alive without disease (except for DI).
[i]DcD, dead with disease.
[j]Patient received concurrent cytotoxic chemotherapy.

fined as a decrease in ADH replacement dose) in 19% [10]. The median dose was 1,200 cGy. Eight of the patients received multiple courses of treatment, presumably for lack of initial response. Three of the four complete responders received radiation within one week of diagnosis. The interval from onset of symptoms to treatment was not discussed. In seven patients who did not receive radiation treatment for DI, there were no responders.

In a study at the Hospital for Sick Children (London), 21 children with LCH, but without DI were prospectively followed for DI by measuring the response of urinary arginine vasopressin (a more sensitive test of DI than urine osmolality) to water deprivation [5]. Five children (24%) had abnormal responses on initial testing, and two of these children subsequently developed DI, as compared to only one of the sixteen children with normal responses to water deprivation. Two of these three children were subsequently irradiated with no relief of symptoms. One of the children who had an initially abnormal water deprivation test subsequently had improvement on retesting after etoposide therapy.

Minehan et al. [6] evaluated 30 patients with LCH-DI treated with hypothalamic-pituitary radiation therapy at the Mayo Clinic. Of 28 evaluable patients, 17% had a CR and 3% had a PR. Five of the six responders received radiation within 14 days of diagnosis. Many patients responded greater than 5 years after radiation therapy. Although there was no clear dose-response in the treatment of DI, a higher percentage of patients treated with greater than 15 Gy (60%) had response as compared to patients treated to less than 15 Gy (30%).

In the present series, 2 of the 14 patients (14%) treated with HPRT developed a complete response. Of interest, neither patient had a full ADH deficiency. One patient had a normal water deprivation study shortly before he developed increased polyuria and polydipsia and was treated on clinical grounds. The other responder had a partial ADH deficiency based on urine and serum osmolality testing. One of the patients was treated with the highest radiation dose (1,800 cGy) used in our series.

Minehan et al. [6] reported complete radiographic response (normalization of CT or MRI) in one patient and partial radiographic response in three patients treated with HPRT. These four patients were considered to be responders to radiation although none of these patients had a clinical response. All radiographic responders re-

TABLE II. Review of Clinical Studies of Hypothalamic-Pituitary Irradiation for the Treatment of Langerhans' Cell Histiocytosis-Induced Diabetes Insipidus

Study (years)	No. pt. LCH[a]	No. pt. DI[b]	No. pt. HPRT[c]	Med F/U[d]	Median dose (fx)[e]	Median sx → rx[f]	Median dx → rx[g]	Clinical CR	Clinical PR[h]	Ref[i]
Harvard (1918–75)	127	28	21	8.5 yr	1,200 (6)	—	1 mo	19%	19%	10
Hospital for Sick Children, London (1985–88)	52	15	2	short	1,200 (8)	5 mo	3 wk	0%	0%	5
Mayo Clinic (1950–89)	1,200	47	30	14.7 yr	1,100 (8) 500–	70 d	6 d	17%	3%	6
Minnesota (1954–72)	30	N/A[j]	7	—	1,830	—	—	0%	0%	13
Children's Hospital of Philadelphia (1970–84)	78	8	4	—	<1000	—	—	0%	0%	14
UCLA	—	13	3	—	1,200	—	—	0%	0%	7
Harvard (1975–90)	116	17	14	7.3 yr	750 (3)	30 d	4 d	14%	0%	present series

[a]No. pt. LCH, number of patients with Langerhans' cell histiocytosis.
[b]No. pt DI, number of patients with LCH-induced diabetes insipidus.
[c]No. pt. HPRT, number of patients who received hypothalamic-pituitary radiation therapy.
[d]Med F/U, median follow-up.
[e]fx, number of fractions, dose is given in cGy.
[f]Sx → Rx, symptoms to treatment interval.
[g]Dx → Rx, diagnosis to treatment interval.
[h]CR, complete response; PR, partial response.
[i]Ref, reference number.
[j]N/A, not applicable.

ceived RT. Therefore, it seems that radiographic response may not be a clinically relevant endpoint.

Complications

Complications of hypothalamic-pituitary radiation therapy in the Mayo Clinic series include endocrine abnormalities (either growth hormone deficiency or panhypopituitarism) in 43% of patients who received radiation. Of the 16 patients who received no radiation therapy to the pituitary area, only one (6%) developed a subsequent endocrinopathy [6]. Greenberger et al. [10] did not discuss complications from radiation therapy. Seventeen of 55 long-term survivors reported by the Southwest Oncology Group had neuropsychiatric disorders other than DI. Sixty-two percent of these patients had received radiation therapy to the cranium. Findings in children with LCH include emotional difficulties, poor school performance, and delayed motor development [15].

The present series reports panhypopituitarism in two patients treated with HPRT. It is unclear whether hypopituitary dysfunction is related to the initial disease process or to the radiation therapy. Even at low doses, radiation to an already susceptible hypopituitary axis might leave these patients more prone to endocrinopathies. The astrocytoma that occurred in one child would not be considered a radiation-induced tumor secondary to the short interval between therapy and tumor development [16]. There were no long-term neuroendocrine complications other than DI in the three patients with LCH-DI who did not receive HPRT.

CONCLUSIONS

The results at our institution are similar to results observed in other published series of patients with LCH-DI treated with HPRT [6,10]. However, unlike the previous conclusions from our center, we now recommend a more conservative approach. The data in the current report show that only the two responders had ''early'' disease as evidenced by lack of a full ADH deficiency on water deprivation tests. This suggests that treatment might be more effective when it is given promptly, perhaps before irreversible damage is done to the hypothalamus. Our current treatment strategy entails close monitoring of patients with LCH for symptoms of DI, especially in patients with radiographic abnormalities in the hypothalamic-pituitary axis, as this has been shown to correlate with the development of DI [5,17–19]. In those patients with polyuria or polydipsia and any abnormality on water deprivation studies, rapid treatment with HPRT appears justified. Treatment could be done using stereotactic or conformal radiotherapy techniques, which would limit the dose to normal brain tissue. Unlike previous reports, there does not appear to be any rationale for treating patients with full ADH deficiency, as there is no evidence that these patients with ''late'' disease will respond to therapy.

Although there is some evidence that a higher radiation dose might yield improved response, the data on this matter are not conclusive. As LCH typically does not show a dose response, the use of higher doses, especially in the setting of possible long-term complications as a

result of treatment, needs further study in order to be recommended.

ACKNOWLEDGMENTS

The authors thank J.R. Cassady for the management of many of the patients. We thank C.N. Coleman for his support.

REFERENCES

1. Komp DM: Concepts in staging and clinical studies for treatment of Langerhans' cell histiocytosis. Semin Oncol 18:18–23, 1991.
2. Willman CL, Busque L, Griffith BB, Favara BE, McLain KL, Duncan MH, Gilliland DG: Langerhans'-cell histiocytosis (histiocytosis x)—a clonal proliferative disease. N Engl J Med 331:154–160, 1994.
3. Yu RC, Chu C, Buluwela L, Chu AC: Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet 343: 767–768, 1994.
4. Langerhans' cell histiocytosis. In Halperin EC, Constine LS, Tarbell NJ, Kun LE (eds): ''Pediatric Radiation Oncology'' (ed. 2). New York: Raven Press, 1994, pp. 446–72.
5. Dunger DB, Broadbent V, Yoeman E, et. al.: The frequency and natural history of diabetes insipidus in children with Langerhans' cell histiocytosis. N Engl J Med 321:1157–1162, 1989.
6. Minehan KJ, Chen MG, Zimmerman Seckl JR, Lightman SL, Grant DB, Pritchard J: Radiation therapy for diabetes insipidus caused by Langerhans' cell histiocytosis. Int J Rad Oncol Bio Phys 23:519–524, 1992.
7. Braunstein GD, Kohler PO: Endocrine manifestations of histiocytosis. Am J Ped Hem/Oncol 3:67–75, 1981.
8. Greenberger JS, Crocker AC, Vawter G, Jaffe N, Cassady JR: Results of treatment of 127 patients with systemic histiocytosis (Letterer-Siwe syndrome, Schüller-Christian syndrome and multifocal eosinophilic granuloma). Medicine 60:311–338, 1981.
9. McLelland J, Pritchard J, Chu AC: Current controversies histiocytosis x. Hematol Oncol Clin Nortn Am 1:147–162, 1989.
10. Greenberger JS, Cassady JR, Jaffe N, Vawter G, Crocker AC: Radiation therapy in patients with histiocytosis: Management of diabetes insipidus and bone lesions. Int J Rad Oncol Bio Phys 5:1749–1755, 1979.
11. Osband ME, Lipton JM, Lavin P, Levey R, Vawter G, Greenberger JS, McCaffrey RP, Parkman R: Histiocytosis x: Demonstration of abnormal immunity, T-cell histamine H2-receptor deficiency, and successful treatment with thymic extract. N Engl J Med 304:146–153, 1981.
12. Dealy JB, Sosman M: Irradiation therapy in Hand-Schüller-Christian's disease. Oral Surg Med Pathol 9:1256–1257, 1956.
13. Smith DG, Nesbit ME, D'Angio GJ, Levitt SH: Histiocytosis x: Role of radiation therapy in management with special reference to dose levels employed. Radiology 106:419–422, 1973.
14. Gramatovici R, D'Angio GJ: Radiation therapy in soft-tissue lesions in histiocytosis x (Langerhans' cell histiocytosis). Med Pediatr Oncol 16:259–262, 1988.
15. Komp DM: Long-term sequelae of histiocytosis x. Am J Pediatr Hem/Oncol 3:165–167, 1981.
16. Cavin LW, Dalrymple GV, McGuire EL, Maners AW, Broadwater JR: CNS tumor induction by radiotherapy: A report of four new cases and estimate of dose required. Int J Rad Oncol Bio Phys 18:399–406, 1990.
17. Maghnie M, Arico M, Villa A, Genovese E, Beluffi G, Severi F: MR of the hypothalamic-pituitary axis in Langerhans' cell histiocytosis. AJNR Am J Neuroradiol 13:1365–1371, 1992.
18. Tien RD, Newton TH, McDermott MW, Dillon WP, Kucharczyk J: Thickened pituitary stalk on MR images in patients with diabetes insipidus and Langerhans' cell histiocytosis. AJNR Am J Neuroradiol 11:703–708, 1990.
19. Schmitt S, Wichmann W, Martin E, Zachmann M, Schoenle EJ: Pituitary stalk thickening with diabetes insipidus preceding typical manifestations of Langerhans' cell histiocytosis in children. Eur J Pediatr 152:399–401, 1993.